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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,094	03/27/2001	Richard I. Weiner	UCSF-018/02US	6968

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EXAMINER
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BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Advisory Action</b>	<b>Application N .</b> 09/819,094	<b>Applicant(s)</b> WEINER ET AL.	
	<b>Examin r</b> Michael Brannock	<b>Art Unit</b> 1646	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED **FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.**  
Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY [check either a) or b)]**

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
  - (b) ☐ they raise the issue of new matter (see Note below);
  - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
  - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_.

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☐ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 28.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The proposed drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.
10. ☐ Other: \_\_\_\_\_.

**Attachment to Advisory Action**

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 4189426, to Choh Li, 2/1980, in view of US Patent 4853332, to Mark et al., 8/1989, as set forth previously.

Li disclose the proteolytic N-terminal fragment of human Placental lactogen, a.k.a. human choriomammotropin (HCS), see col 6. consisting residues 1-133, see col 7. The polypeptide of SEQ ID NO: 18, however, has been mutated to replace the reactive cysteine at position 53 and with serine. The reactive cysteine at this position is well known to be involved in a disulfide bond (e.g. see col 7, line 32 of Li). Li teaches that this reactive cysteine be neutralized by rendering it incapable of disulfide bond formation by any means known in the art (see col 1, last paragraph to col. 2). Consequently, Li accomplish this by carboxamidomethylation, e.g. col 2 first paragraph. Subsequently, however, Mark et al. disclose an improved method of preventing undesirable disulfide formation at cysteine residues in peptide hormones, e.g. by mutagenically replacing the reactive cysteine residue with a non reactive residuc (see col 1), e.g. with serine (e.g. col 5 line 23). Additionally, Li teach that the peptide be present in a pharmaceutically acceptable carrier, e.g. 0.1M tris 8.2 (col 4, L8), i.e. for use in the rat tibia test (Example II). The claim has been amended to require that the peptide be present in an angiogenesis amount in a pharmaceutically acceptable carrier. The specification indicates that the peptides can be administered in an extraordinary range of concentrations. At page 11 the specification discloses the following:

10611 Typically, the peptides of the invention are administered in an amount of about 8 micrograms to 3,000 ug/kg per day, and more preferably about 20 to 1,500 ug/kg per day

preferably once or twice daily. However, other amounts, including substantially lower or amounts, may also be administered.

The specification does not set any limit to this range. Based on these teachings, one would thus have to expect that the presence of the protein at practically any concentration would have at least some anti-antigenic effect. Thus, one would also expect that the concentrations taught by U.S. Patent No: 4189426, wherein substantial *in vivo* physiological responses were measured, would also inherently have anti-angiogenic properties, absent evidence to the contrary.

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success, to replace the cysteine residue at position 53 of the 16 kDa fragment of human placental lactogen, as taught by Li, with a serine residue as taught by Mark et al.. The motivation to do so is provided by both Li, who teaches that the reactive 53-cysteine be prevented from bond formation, and by Mark et al. who disclose an improved method to accomplish this in peptide hormones (e.g cols 1 and 2).

Applicant argues that use of 0.1 molar Tris buffer at a pH of 8.2 is not a pharmaceutically acceptable carrier. Further, there is no disclosure within Choh Li suggesting that a peptide such as the peptide of SEQ ID NO.:18 should be placed within a pharmaceutically acceptable carrier. This argument has been fully considered but not deemed persuasive. The peptide was administered *in vivo* by Choh Li by injection, thus one of ordinary skill in the art would appreciate that the carrier used would necessarily be pharmaceutically acceptable. Applicant has provided no reasons as to why this would not be true.

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Applicant's arguments, as they relate mutagenesis are not persuasive and have been substantially addressed previously. Li teaches that the reactive 53-cysteine be prevented from bond formation, and Mark et al. disclose an improved method to accomplish this in peptide hormones (e.g cols 1 and 2). Thus, there is no requirement for a very large amount of mutagenesis, as Applicant asserts.

### *Conclusion*

No claims are allowable.

Please note the new official fax number below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.


Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB



October 28, 2003

  
YVONNE EYLER, PH.D.  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600